Statements under 37 C.F.R. §1.173(c)

The following statements are made pursuant to the requirements of 37 C.F.R. §1.173(c). Patent claims 1-4 have been cancelled without prejudice toward the continuation of prosecution in a continuing application. Added claims 5-176 and 178-209 have also been cancelled without prejudice. Claims 177 and 210-213 are the only claims now pending in the case.

Pursuant to 37 C.F.R. §1.173(c), the following is an explanation of the support of the disclosure of the patent for the changes made to the claims by the present amendment.

Claim 177 has only been amended to change its dependency to be from new claim 210 or 211. Thus, no new limitations were added to these claims and they are supported for the same reasons that they were considered to be supported prior to the present amendment.

New claims 210 and 212 are amalgams of previously appearing claims 174-177, 183-186, 192-195 and 201-204. Claim 210 is rearranged to be directed only to the genetically-engineered antibody embodiment previously claimed in claims 176, 185, 194 and 203. However, the features of the antibody as previously claimed have all been combined into one claim, i.e., the feature of recognition of an epitope within residues 1-28 of beta-amyloid as previously claimed in claims 174 and 192, the feature of being obtainable using residues 1-28 of beta-amyloid as an immunogen as previously claimed in claims 183 and 201, the feature of being able to inhibit aggregation

of beta-amyloid as previously claimed in claims 174 and 183, and the feature of being able to maintain the solubility of soluble beta-amyloid as previously claimed in claims 192 and 201, all appear as alternatives in the single new claim 210 directed to the genetically-engineered antibody embodiment. All of these features are supported for the same reasons that they were considered to have been supported in the previously appearing claims.

Additionally, claim 210 adds the statement that the "genetically-engineered antibody is obtained from a monoclonal antibody …." This statement is supported by the specification at column 10, lines 1-3.

Claim 212 is specifically directed to the human monoclonal antibody embodiment previously claimed in claims 184 and 202. However, the features of the antibody as previously claimed have been combined into one claim, i.e., the feature of being obtainable using residues 1-28 of beta-amyloid as an immunogen as previously claimed in claims 183-184 and 201-202, the feature of being able to inhibit aggregation of beta-amyloid as previously claimed in claims 183-184, and the feature of being able to maintain the solubility of soluble beta-amyloid as previously claimed in claims 201-202, all appear as alternatives in the single new claim 211 directed to the genetically-engineered antibody embodiment. All of these features are supported for the same reasons that they were considered to have been supported in the previously appearing claims.

Claims 210 and 212 have been broken into numbered or lettered subparagraphs so as to avoid any unclarity or ambiguity as to what the alternatives refer.

New claims 211 and 213 claim the subject matter previously claimed in claims 155, 161, 167 and 173, i.e., that the beta-amyloid is human beta-amyloid. These claims are supported for the same reason that claims 155, 161, 167 and 173 were considered to have been supported prior to the present amendment. See also, for example, the present specification at column 12, line 2. Claims 211 and 213 refer back to specific sub-paragraphs of the claim from which each depends, for added clarity.

REMARKS

Claims 177 and 210-213 presently appear in the case. No claims have been allowed. The official action of June 2, 2006, has now been carefully studied. Reconsideration and allowance are hereby respectfully urged.

Briefly, the present invention relates to a therapeutic composition that comprises a pharmaceutical formulation of a pharmaceutically acceptable carrier and a human or genetically-engineered monoclonal antibody or antibody binding fragment thereof. The antibody is one that either inhibits aggregation of β-amyloid or maintains the solubility of soluble β-amyloid. The genetically-engineered antibody is obtained from a monoclonal antibody that either recognizes an epitope within residues 1-28 of β-amyloid or is obtainable using residues 1-28 of β-amyloid as an immunogen. The human monoclonal antibody must be one that is obtainable using residues 1-28 of β-amyloid as an immunogen.

The telephonic interview conducted among Examiner Turner and the undersigned attorney, with Mr. Gordon Kit, attorney for the licensee of this invention, being on the line as an observer, is hereby gratefully acknowledged. Prior to this interview, claims that were substantially the same as presently presented new claims 210 and 212 were provided to the examiner for the purpose of discussion. The undersigned proposed to obviate the rejections based on the examiner's broad interpretation of "genetically-engineered" antibodies by clarifying that genetically-engineered antibodies are obtained

from monoclonal antibodies, as is disclosed on column 10, lines 1-3, of the present specification. As to the rejection of the claims to human monoclonal antibodies over Gaskin, the undersigned explained that we proposed to specify in such claims that the antibodies were obtainable by using residues 1-28 of beta-amyloid as immunogen. Gaskin explicitly states that residues 29-40 play a part in the conformational epitope of its antibodies. Thus, the proposed new claims are also free of Gaskin. With respect to the obviousness rejection, the undersigned explained that Becker had not found the antibody that Becker predicted might have therapeutic utility and there was no motivation to use Bickel or Gaskin as the antibody of Becker as there would be no reason for one of ordinary skill in the art to believe that these antibodies would have the special properties required for Becker's application. Inherency must be certain when used with respect to an obviousness rejection. Finally, the undersigned pointed out that we did not think the finality of the rejection was proper and that we would request that the finality be withdrawn when we filed our response. The examiner promised to carefully consider these arguments when considering our next response. The arguments presented at the interview are substantially repeated below.

Applicant has no record of having received and Examiner Interview Summary Record. It is respectfully requested that one be prepared by the examiner for the record and provided to applicant.

The Office action of June 2, 2006, was made final despite the presence of new rejections not necessitated by applicant's amendments to the claims. Accordingly, the finality of this action was premature and withdrawal of the finality is respectfully requested. Specifically, the 35 U.S.C. §112, second paragraph, rejection was not entirely necessitated by applicant's amendment of the claims. The objectionable language "said monoclonal and said fragment" was unchanged from the previous version of the claim. This rejection could have been made previously and accordingly the amendment to the claims cannot justify making this new rejection final at this time. Furthermore, claims 155, 161, 167, 176, 185, 194 and 203 were never previously rejected as being anticipated by Bickel. The change of the dependency of claims 155, 161 and 167 did not necessitate this rejection. If the rejection is applicable now, it would have been just as applicable at the time of the last Office action. The examiner's position that a monoclonal antibody is a genetically-engineered antibody was made for the first time in the final rejection and that is why claims 176, 185, 194 and 203 were rejected over Bickel for the first time. However, no substantive changes were made to these claims that might have necessitated this new rejection. The same applies to the rejections of these claims over Stern and Walker.

MPEP §706.07(a) states:

> Under present practice, second or any subsequent actions on the merits shall be final, except where the examiner

> introduces a new ground of rejection that is neither necessitated by applicant's amendment of the claims nor based on information submitted in an information disclosure statement filed during the period set forth in 37 CFR 1.97(c) with the fee set forth in 37 CFR 1.17(p).

Accordingly, the finality of this rejection was premature. Reconsideration and withdrawal thereof is respectfully urged.

The Information Disclosure Statement filed herewith is based on the assumption that the finality of the last rejection will be withdrawn as requested above.

MPEP §1453.V.D. states with respect to the amendment of new claims:

> Although the presentation of the amended claim does not contain any indication of what is changed from the previous version of the claim, applicant must point out what is changed in the "Remarks" portion of the amendment.

Claim 177 is a previously presented new claim in the sense that it was not present in the patent as issued and is being amended by the present amendment. The only change made in claim 177 is that this claim was previously dependent on claim 176 and is now dependent on claim 210 or 211. Claims 210-213 are new claims and were not previously presented. However, the differences between these new claims and the previously presented claims are discussed in the section containing statements under 37 C.F.R. §1.73(c), hereinabove.

Applicant notes with appreciation the examiner's recognition that all objections and rejections not reiterated in the official action of June 2, 2006, have been withdrawn by the examiner.

The examiner has advised applicant that page 2 of the 1449 submitted on August 29, 2002 is missing from the office file. The examiner has requested, if a signed copy of this page has previously been provided to applicant, that a copy thereof be submitted to the Office for completion. If the signed copy has not been transmitted to applicant, the examiner requests that an unsigned copy be submitted for consideration.

Applicant's records show no IDS filed on August 29, 2002. However, one was filed on August 22, 2002, but with only one page of form 1449. A copy of this 1449 with the initials of an examiner has been found in the file of the undersigned and a copy is attached hereto. It also appears in the PTO PAIR file for this case as the second page of 12 of the IDS entry of June 10, 2004. It is requested that the references on this form be included on the face of any patent issuing from this application. We note that, while all of the foreign patent and NPL references listed on this form appear in the PTO Image File Wrapper on PAIR, the entire IDS appears to be missing. To complete the record, attached is another complete copy of the IDS filed on August 22, 2002, without refiling the references, along with a copy of the post card filing receipt.

The examiner has reminded applicant of the continuing obligation under 37 C.F.R. §1.178(b) to timely apprise the Office of any prior or concurrent proceeding in which Patent No. 09441140 (presumably the examiner meant to

refer to patent no. 5,688,651) is or was involved, including interferences, reissues, reexaminations and litigation.

No such proceeding is in existence. However, the examiner's attention is invited to the fact that a divisional application from this reissue application was filed on February 22, 2006, and has received application no. 11/358,951.

Applicant has further been reminded of the continuing obligation under 37 C.F.R. §1.56 to timely apprise the Office of any information which is material to patentability of the claims under consideration in this reissue application.

Applicant continually bears this obligation in mind. An IDS is attached hereto. As indicated above, it is based on the assumption that the finality of the previous rejection will be withdrawn.

The examiner is reminded of her obligation to cite of record in a PTO-892 all of the prior art that was cited of record in the prosecution of the patent of which this application is a reissue (5,688,651). See MPEP 1406. Applicant requests that the examiner do so.

Claims 155, 161, 167, 173-177, 183-186, 192-195 and 201-204 have been rejected as being based upon a defective reissue oath under 35 U.S.C. §251 as the claims have been significantly amended since the filing of the previous oath. A supplemental reissue declaration in compliance with both 37 C.F.R. §1.175(b) and (c) has been required.

A new supplemental reissue declaration is attached hereto, thus obviating this rejection.

Claims 155, 161, 167, 173-177, 183-186, 192-195 and 201-204 have been rejected under 35 U.S.C. §112, second paragraph, as being indefinite. The examiner says that base claims 174, 183, 192 and 201 recite alternative elements of the claim where the alternatives are indefinite as it is unclear if applicant's intention is to recite elements A and B together and C separately, or alternatively elements A and B together and elements A and C together. Other areas of alleged ambiguity have also been pointed out. The examiner says that the scope of the claim with respect to its required and alternative elements should be clarified.

New claims 210 and 212 have been rewritten with this rejection in mind so as to be very clear as to what alternatives are being covered. To do so, the claim has been broken into numbered or lettered subparagraphs so that it can clearly and unambiguously be seen what the alternatives refer to. Accordingly, it is believed that this rejection has now been obviated. If the examiner believes that there is still any indefiniteness in the present claims, she is requested to contact the undersigned by telephone so as to work out wording that would be acceptable under the second paragraph of 35 U.S.C. §112.

Claims 155, 161, 167 and 173 have been rejected as being further indefinite with respect to the recitation "wherein said beta-amyloid is human beta amyloid" as the base

claims refer to both (i) residues 1-28 of beta amyloid and to (ii) either the inhibition of aggregation of beta amyloid or the maintenance of solubility of beta amyloid. The examiner thus does not consider it clear as to which amino acid sequences/residues and what properties the claims are reciting/limiting. Clarity has been required.

Claims 155, 161, 167 and 173 have now been deleted in favor of new claims 211 and 213. These new claims now make very clear that every reference to "beta-amyloid" in the base claim is specified as "human beta-amyloid" in the dependent claim. For further clarity, each of these claims now refer to specific sub-paragraphs of the claim from which it depends. Accordingly, this part of the rejection has now been obviated. Reconsideration and withdrawal thereof is therefore respectfully urged.

Claims 155, 161, 167, 173-174, 176, 183, 185, 192, 194, 201 and 203 have been rejected under 35 U.S.C. §102(a) as being anticipated by Bickel, as further evidenced by Solomon 2002. The examiner states that while Stern does evidence that Bickel's AMY33 is a mouse monoclonal, this antibody applies as a genetically-engineered monoclonal antibody and it also applies as comprising an antigen binding fragment thereof. The same claims were also rejected under 35 U.S.C. §102(a) as being anticipated by Stern, as further evidenced by Solomon 2002, for essentially the same reasoning as explained with respect to the anticipation rejection over Bickel. These rejections are respectfully traversed.

Claim 210 has now been presented in order to clarify the intent of the term "genetically-engineered antibody" and so as to make very clear that this term does not read on a conventionally obtained monoclonal antibody. One must first have a monoclonal antibody before one can genetically-engineer it into another form, such as a single chain antibody. Support for this clarification, as is now present in claim 210, is found on column 10, lines 1-3, of the present specification. Note that the present specification makes reference to Haber, "Engineered Antibodies as Pharmacological Tools", *Immunological Reviews*, 130:189-212 (1992) at col. 2, lines 59-63, and col. 16, lines 27-33. While Haber was cited of record during the prosecution of the patent of which this is a reissue application, another copy is attached hereto for the examiner's ease of consideration. It is also included on the IDS submitted herewith. Thus, techniques for forming genetically-engineered antibodies from monoclonal antibodies were well known as of the effective filing date of this application, as is evidenced by the present specification.

It should now be very clear that the present claims do not encompass murine monoclonal antibodies not subjected to genetic engineering. The present claims, which are supported by the present specification, are thus not anticipated by Bickel or Stern, which only teach murine monoclonal antibodies. As will be discussed below, there is no motivation in these references or any other art of record to perform genetic engineering on such antibodies. Accordingly,

reconsideration and withdrawal of this rejection are respectfully urged.

Claims 155, 161, 167, 173-176, 183-85, 192-194, and 201-203 have been rejected under 35 U.S.C. §102(b) as being anticipated by Gaskin as evidenced by Solomon. The examiner states that Gaskin teaches four human monoclonal antibodies that bind epitope 1-28 of human Aβ. The examiner states that Gaskin evidences that the antibodies react to Aβ 1-28 and no other proof is needed. The examiner says that the recitation that the antibody "may be obtained by" is a product-by-process limitation not garnering weight where the prior art antibody is already evidenced to provide the recited structural constraints of binding to Aβ 1-28. This rejection is respectfully traversed.

New claims 212 and 213 are now directed to the human monoclonal antibody embodiment. Both claims require that the human monoclonal antibody be "obtainable using residues 1-28 of beta-amyloid as an immunogen." Regardless of whether this is considered to be a product limitation or a product-by-process limitation, it is clear from the language of Gaskin itself that none of the antibodies of Gaskin could possibly have been obtainable using Aβ 1-28 as an immunogen. Gaskin explicitly states at page 1184, right column, in the sentence before the Discussion section:

> The results from the two inhibition assays document that there is a significant contribution to the reactive epitope by the sequence 29-40 in the β-A_{1-40}.

The second paragraph of the Discussion section, in the same column states:

> The nature of the reactive epitope was explored. The reactive epitope appears to reside in the region of amino acids 1-28 of the β-A_{1-40}. Further analysis suggests that the reactive epitope is conformational in that there is a significant contribution to the antigenic determinant by the region 29-40. In comparison with β-A_{1-40}, four- to eightfold greater concentrations of β-A_{1-28} were required in immunohistochemical studies to block the staining of amyloid plaque. It appears that the conformational nature of the reactive epitope is conserved in the amyloid plaques in situ. This epitope also differs from those recognized by xenogeneic antibodies raised against β-A_{1-28} (10-12). Thus, these antibodies recognize a unique epitope on the β-AP and their reaction represents an added example of uniqueness of epitopes reactive with autoantigens. [Emphasis added]

The fact that the region 29-40 makes a significant contribution to the antigenic determinant and that the epitope differs from those recognized by xenogeneic antibodies raised against Aβ 1-28 conclusively establishes that the epitope could not have been obtainable using only residues 1-28 of human β-amyloid as an immunogen. Accordingly, none of the present claims are anticipated by Gaskin. Reconsideration and withdrawal of this rejection are therefore respectfully urged.

Claims 155, 161, 167, 173-174, 176, 183, 185, 192, 194, 201 and 203 have been rejected under 35 U.S.C. §102(a) as being anticipated by Walker as evidenced by Solomon. The examiner states that the process of making monoclonal antibodies is the result of genetic engineering and thus the

10D5 antibody of Walker is a genetically-engineered antibody. This rejection is respectfully traversed.

As discussed above with respect to the rejections over Bickel and Stern, the present claims now specify that the genetically-engineered antibodies are obtained from monoclonal antibodies. Thus, the present claims directed to genetically engineered antibodies no longer read on conventional monoclonal antibodies . Accordingly, this rejection has now been obviated. Reconsideration and withdrawal thereof are respectfully urged.

Claims 155, 161, 167, 173-177, 183-186, 192-195 and 201-204 have been rejected under 35 U.S.C. §102(b) as being anticipated by, or in the alternative 35 U.S.C. §103(a) as being obvious over Becker in view of Bickel or Gaskin. The examiner states that Becker teaches pharmaceutical formulations containing antibodies having specificity for β-amyloid peptide and that the peptides contain just the first 40 amino acids of the β-amyloid peptide. The examiner states that the reference teaches antibodies and fragments of antibodies, including chimeric, humanized, veneered, resurfaced or CDR-grafted antibodies, single-chain antibodies, as well as human monoclonal antibodies and genetically-engineered monoclonal antibodies. The examiner states that the antibodies disclosed are presumed to recognize an epitope within 1-28 of β-amyloid or to be obtainable using residues 1-28 of β-amyloid as an immunogen. The examiner states that it would have been obvious to use the antibodies of Bickel and

Gaskin to produce pharmaceutical formulations wherein the antibody is genetically-engineered or a single-chain antibody as taught by Becker and well-established in the art. The examiner states that the reliance on the combination is merely noted for more specific genetic modification of the art known antibodies, which is supplied by Becker. This rejection is respectfully traversed.

Becker is a totally theoretical disclosure without a shred of experimental evidence disclosed therein. It notes, without disclosing specific results, that β-amyloid which has assumed a predominantly β-sheet conformation is more neurotoxic *in vitro* than β-amyloid that is predominantly in random coil or α-helix configuration. See col. 5, lines 27-33. Becker then discloses the desirability, at least for diagnostic purposes, of finding conformationally specific antibodies that show a high level of specificity for the β-amyloid peptide in a specific conformation, while showing markedly less specificity for the same peptide having a different secondary structure. See col. 6, lines 22-30. Becker considers its invention, insofar as antibodies are concerned, to relate to both antibodies that bind only those β-amyloid peptides which are predominantly in a β-sheet conformation, as well as to antibodies that bind only those β-amyloid peptides which have adopted a random coil or α-helix conformation. See col. 5, lines 45-50, and col. 7, lines 26-38. The antibodies are generally described as being "used in diagnostics, therapeutics or in diagnostic/therapeutic

combinations." See col. 7, lines 39-40. The antibodies are disclosed as being useful in the "diagnosis and/or treatment of Alzheimer's disease in mammals, preferably humans." See col. 7, lines 49-52. Which one (or both) of the two classes of disclosed antibodies are useful for any kind of therapeutic application is not said in the specification, nor is there any explanation of why they might be useful therapeutically. The claims also shed no light on which antibodies might be therapeutically useful, or why.

No antibodies having the wished-for conformationally-specific properties are disclosed in Becker, nor is it certain that any such antibodies exist or even can exist. No rationale is given for the conclusion that, even if such antibodies were isolated, they would be therapeutically useful. There is no suggestion that they would lessen toxicity or would prevent aggregation or would cause disaggregation. The disclosure of Becker is nothing more than a wish to find antibodies of specific properties and a hope that they may somehow be therapeutically useful. Nobody of ordinary skill in the art would know why such antibodies would be useful therapeutically. Thus, there is no motivation to try to find such antibodies.

The examiner is apparently taking the position that the antibodies of Bickel and Gaskin must inherently either have conformational specificity for β-amyloid peptide in the β-sheet conformation with lack of specificity for β-amyloid peptide in the random coil or α-helix conformation, or *vice*

versa. But there is absolutely nothing in either Bickel or Gaskin that would suggest that those antibodies have these very special properties. They were certainly not elicited by means of the screen disclosed at col. 6, lines 22-30, of Becker. Obviousness cannot be predicated on what is not known at the time the invention is made, even if the inherency of a certain feature is later established (the latter not being the case here). *In re Rijckaert*, 9 F.2d 1531, 28 USPQ2d 1955 (Fed. Cir. 1993). See MPEP 2141.02V.

To the extent that the rejection is turned around to try to use Becker to establish the obviousness of genetically-engineering the antibodies of Bickel and Gaskin, as is also suggested by the rejection, this also fails. There is no motivation provided by either Bickel or Gaskin to use the antibodies thereof therapeutically. For the reasons discussed above, Becker does not provide that motivation as there is absolutely no reason for one of ordinary skill in the art to believe that the antibodies of Bickel or Gaskin are specific only to the β-sheet conformation or specific only to the random coil or α-helix conformation.

The examiner states that it has already been established that the Bickel and Gaskin antibodies "are of the correct epitope specificity" (page 15 of the Official action). However, the examiner is here speaking of the epitope specificity of the present claims, not the correct epitope specificity required by Becker for therapeutic efficacy. The present specification is not prior art. The prior art must

provide the motivation for combining references. In order to allege that Becker makes obvious using the antibodies of Bickel or Gaskin therapeutically, the examiner must establish that such antibodies have the epitope specificity required of Becker (not as required by the present claims). Only then can Becker be used as part of an obviousness rejection as allegedly making it obvious for one of ordinary skill in the art at the time the invention was made to genetically-engineer the antibodies of Bickel or Gaskin. As Bickel and Gaskin suggest no therapeutic utility, there is no motivation to provide reduced hyperimmunogenicity, antigenic specificity, etc., as suggested by the examiner at page 16 of the Office action.

It is well established that a reference must contain an enabling disclosure in order to be available as a reference under 35 U.S.C. §102, *In re Hoeksema*, 399 F2d 269, 158 USPQ 596 (CCPA 1968). See MPEP §2121.01. It is true that MPEP §2121 states that when the reference relied on expressly anticipates or makes obvious all of the elements of the claimed invention, the reference is presumed to be operable, and the burden is on applicant to provide facts rebutting the presumption of operability. However, as discussed above, Becker does not expressly anticipate, nor does it make obvious all of the elements of the claimed invention. Furthermore, a mere review of the Becker specification, without any examples or even any theory of operability, would establish *prima facie*

that it neither teaches how to make or how to use the antibodies wished for by Becker.

Accordingly, no combination of Becker, Bickel and Gaskin would suggest that the antibodies of Bickel and Gaskin might be therapeutically useful for any reason and therefore there would be no motivation to genetically-engineer such antibodies. Reconsideration and withdrawal of this rejection are therefore respectfully urged.

It is submitted that all of the claims now present in the case clearly define over the references of record and fully comply with 35 U.S.C. §112. Reconsideration and allowance are, therefore, earnestly solicited.

Respectfully submitted,
BROWDY AND NEIMARK, P.L.L.C.
Attorneys for Applicant(s)

By /rlb/
Roger L. Browdy
Registration No. 25,618

RLB:rd
Telephone No.: (202) 628-5197
Facsimile No.: (202) 737-3528
G:\BN\R\ramq\Solomon1R\Pto\AmendmentJ.doc